30. (New) A method of detaching a nucleic acid molecule from a solid support to which it is attached, wherein an unconventional nucleotide is incorporated a predetermined site in said nucleic acid molecule, said method comprising selectively cleaving said nucleic acid molecule at the site of said unconventional nucleotide, or of reversibly immobilizing a nucleic acid molecule, said method comprising:

(a) incorporating an unconventional nucleotide into said nucleic acid molecule at a pre-determined site;

(b) binding said nucleic acid molecule to a solid support; steps (a) and (b) being carried out in either order or simultaneously; and subsequently

(c) selectively cleaving said nucleic acid molecule at the site of said unconventional nucleotide, as claimed in claim 1 or 2, or a method as claimed in claim 19,

wherein a multiplicity of different nucleic acid molecules or chimeric molecules comprising a nucleotide linker sequence comprising a selectively cleavable unconventional nucleotide at a pre-determined site, coupled to a functional group, are attached or bound to a solid support, each said different molecule incorporating a different unconventional nucleotide.

REMARKS

Support for new claims 29 and 30 can be found in original claims 19 and 20.

Claims 19 and 20 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite by including the word "preferably." Applicants respectfully submit that they have obviated this rejections by the amendment set forth above to each of claims 19 and 20.

Claims 1-17, 20 and 22-28 have been rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent 5,700,642, issued to Monforte et al., in view of U.S. Patent 5,985,619, issued to Sutherland et al. the examiner asserted that the '642 patent teaches a method of detaching a nucleic acid molecule from a solid support to which it is attached wherein an unconventional nucleotide is incorporated at a predetermined

site in the nucleic acid molecule, the method comprising selectively cleaving the nucleic acid molecule at the site of the unconventional nucleotide. He acknowledged that the '642 patent does not teach the selective cleaving of the nucleic acid molecule at the site of the unconventional nucleotide, wherein the selective cleavage is accomplished enzymically using a uracil DNA glycosylase enzyme, but he asserted that this is taught by the '619 patent. He asserted that it would have been obvious to one of ordinary skill in the art to combine and substitute the selective cleaving of the nucleic acid molecule at the site of the unconventional nucleotide, wherein the cleavage is accomplished enzymically using a uracil DNA glycosylase enzyme, since the '619 patent states that the glycosylase useful in the present invention is one 'that specifically cleaves unconventional bases" and that the most preferred glycosylase is UNG. This rejection is traversed.

The '642 patent discloses the construction of immobilized or immobilizable selectively cleavable primers which have been modified so as to incorporate a cleavable moiety or cleavable site at or near the 3' end of the primer in order that selective cleavage at that site can be obtained. Although the patent discloses the possibility of ribose being used to provide a selectively cleavable site, enzymatic cleavage is not disclosed in this context in the patent. Rather, the cleavage of the site between the solid support and the primer is stated to be carried out by non-enzymatic means. Indeed, the "cleavage site" is defined in such terms. The examiner is requested to consider column 7 of the '642 patent, wherein a cleavable site is defined as being located at or within about 5 nucleotides from the 3' end of the primer and selectively cleavable by appropriate non-enzymatic means, including chemical, thermal or photolytic means. (column 7, line 52 et seq.) It further is requested that the examiner turn his attention to column 14, lines 50-59, wherein cleavage of ribose sites is said to be carried out by "treatment with dilute ammonium hydroxide."

Accordingly, as the '642 patent specifically teaches away from cleavage by enzymatic means and the claims of the present application are limited to cleavage by

enzymatic means, the teachings of the '642 patent are not applicable to the present invention.

Further, the examiner appears to be of the opinion that the '642 patent teaches a method in which the unconventional nucleotide may be not only a ribonucleotide but, more specifically, a uracil. This interpretation is incorrect. Column 11, lines 5-13, provides only that a cleavable site can be inserted at C(5) of uracil and N(4) of cytosine since these two base sites are readily chemically manipulated and is not a disclosure of the cleavage site being a uracil base. Clearly, this is not a disclosure of cleavage by a glycosylase.

The '619 patent does not compensate for the deficiencies of the '642 patent. The '619 patent discloses a PCR method in which glycosylase is used to reduce the formation of non-specific amplification nucleic acids. Thus, this patent simply concerns the well-known use of UDG/uracil incorporation in decontamination of PCR reactions, i.e., carry-over prevention. In such a situation, uracil is incorporated in a non-specific manner into unwanted PCR products which then are cleaved. There is no suggestion at all in this reference of incorporating uracil at particular predetermined sites to enable selective cleavage at particular positions–all that the decontamination procedure requires is for the unwanted products to be digested away. Selective site-specific cleavage, in terms of defining a particular predetermined selective cleavage site is not an issue in this reference.

Furthermore, the '619 patent does not disclose ro suggest cleavage from a solid support using any enzyme, much less a glycosylase. A person skilled in the art would not be motivated to combine the teachings of the two patents, since the primary reference only suggests selective non-enzymatic cleavage from solid supports and the secondary reference deals with enzymatic cleavage in a non-specific context and not involving solid supports. The non-conventional nucleotides discussed in the '642 patent would not be capable of selective cleavage by a DNA glycosylase enzyme. There is no reason why a person skilled in the art in possession of the '642 patent would use enzymatic cleavage when non-enzymatic cleavage clearly is favored, let

alone use the glycosylase enzyme of the '619 patent. The two patents are directed to completely different problems and the '619 patent does not address the issue of reversible immobilization on, or detachment from, a solid support. Indeed, the use of a glycosylase for the method in the '619 patent results in the production of multiple undefined fragments, unlike the present invention, where specific cleavage is required. The examiner thus can make his arguments only with the aid of hindsight, and it is well-recognized that hindsight is not a permissible basis for considering the obviousness of an invention. See *Gore v. Garlock*, 220 USPQ 303 (F. Cir., 1983): "to imbue one of ordinary skill in the art with knowledge of an invention ... when no prior art reference or references of record convey or suggest that kind of knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *Id.* at 313.

Claims 18 and 19 have been rejected under 35 U.S.C. 103(a) over the '642 and '619 patents, as applied in the preceding rejection, taken further in view of U.S. Patent 5,646,001, issued to Terstappen et al. The examiner acknowledged that the primary and secondary references do not teach a method for separating a target cell from a sample through binding the target cell to a solid support by means of a chimeric molecule comprising a nucleotide linker sequence comprising a selectively cleavable unconventional nucleotide at a pre-determined site, coupled to a functional group, wherein the functional group is an affinity binding group or antibody which binds specifically to the cell. He asserted, however, that the '001 patent teaches such a method and that it would have been obvious to combine the teachings of the references since the '001 patent states that the method disclosed therein has "medically diagnostic and therapeutic applications, as entire cell types can be separated from non-malignant medically vital cell types" and a variety of diseases can be monitored. He stated that one of ordinary skill would have been motivated to combine the teachings of the references in order to achieve the express advantages noted in the '001 patent. This rejection is traversed.

The deficiencies of the '642 and '619 patents have been discussed above, and that discussion is equally applicable to the present rejection. A person of skill in the art would not have been motivated to combine the teachings of the primary and secondary references, and even if the references were combined they would not lead one to the present invention. The '001 patent, which teaches a method for separating a target cell from a sample, wherein a target cell is bound to a solid support via a chimeric molecule, does not compensate for the deficiencies of the primary and secondary references.

Claim 21 has been rejected under 35 U.S.C. § 103(a) over the '642 and '619 patents as applied above and further in view of the Stratagene Catalog. The examiner acknowledged that the primary and secondary references do not teach the motivation to combine all the assay reagents for detecting an analyte in a sample in the form of a kit but asserted that the tertiary reference provides that motivation. This rejection is traversed.

As Applicants have explained above, the assay method of claim 1 is not obvious in view of the cited primary and secondary references, as the references do not fairly suggest the claimed invention. As the method is not obvious, a kit containing the components for carrying out that method also is not obvious. The Stratagene catalog cited by the examiner generally provides that it can be advantageous to provide reagent components in the form of a kit . As the reference does not teach or suggest anything about the particular components useful for carrying out the method of the invention, and the primary and secondary references also do not teach or suggest that method, there is no teaching or suggestion of the components to be provided in a kit for use in the method of this invention. The claimed kit, therefore, is not obvious in view of the teachings of these three references.

Applicants respectfully submit that the pending claims are allowable in view of the foregoing amendments and discussion.

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